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N-Isopropylsulfinylimines as Useful Intermediates in the Synthesis of Chiral Amines: Expeditive Asymmetric Synthesis of the Calcimimetic (+)-NPS R-568

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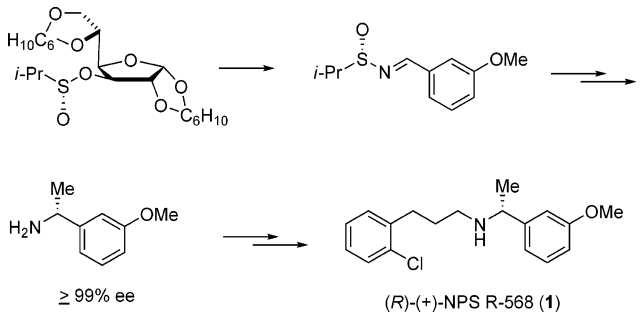

An efficient and high-yielding approach for the asymmetric synthesis of calcimimetic (+)-NPS R-568 (**1**) has been developed. The key step of the synthesis is the highly diastereoselective addition of methyl Grignard to the (S_S,*E*)-*N*-(3-methoxybenzylidene)-2-propanesulfinamide **[5(*S*)]**, which afforded a single diastereoisomer in high yield in short reaction time

The so-called chiral market is in continuous increase as a consequence of the significance of enantiopure compounds in important areas such as agriculture, fragrance, and medicine. As illustrative data, more than 50% of the drugs currently in the market are enantiopure compounds, and the main biologically significant molecules needed for basic biomedical studies, possesses at least one chiral center.[1] Among the biologically significant chiral compounds, those having an amine function occupy a prominent place, as they actually account for 75% of the total of drugs or drug candidates. It is thus not surprising that the development of effective approximations for the synthesis of amines with an α-chiral center has been a standing area of interest in the last decades.[2−6] One of the major breakthroughs in this endeavor has been the development of efficient methods for the synthesis of sulfinamides and the corresponding sulfinylimines. Accordingly, the exceptional behavior of the chiral sulfinyl group in sulfinylimines, as activator, chiral controller, and finally as useful protective group, makes the sulfinamides an extremely versatile chiral intermediate in the construction of chiral amines.[3] Up to now, the most widely used sulfinylimines are the *p*-toluenesulfinylimines **I** pioneered by Davis[4] and the *tert*-butylsulfinylimine **II**, developed by Ellman.[5] While both synthons have been successfully used in the synthesis of a large number of biologically significant amine-containing compounds, the use of the *p*-toluenesulfinyl group as an imine substituent presents some drawbacks. Accordingly, of interest to this work, the addition of small organometallic reagents such as methylmagnesium bromide were reported to attack the sulfur atom, while stabilized organometallic reagents, such as benzylmagnesium chloride, were reported to add only with moderate selectivity.

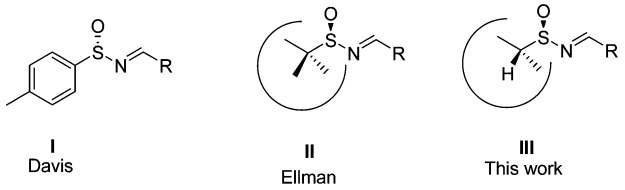

FIGURE 1. *N*-Sulfinylimines.

On the other hand, while the use of the most sterically hindered *tert*-butylsulfinyl group as imine substituent solves most of these drawbacks, there are cases where the reaction became exceedingly slow if not inhibited (vide infra).[6] We have recently introduced the lower molecular weight, highly reactive isopropylsulfinyl derivative **III** as a new imine substituent, with improved diastereoselectivity and reactivity (Figure 1). Accordingly, in a previous work we have shown that the isopropylsulfinyl group do confer better enantiomeric discrimination than the *p*-tolylsulfinyl group and higher chemical reactivity with equal or even better enantiomeric discrimination than the most popular *tert*-butylsulfinyl group in two important reactions, the Corey−Chaykovsky reaction of chiral sulfinylimine and the organocatalytic allylation of acyl hydrazones with ferrocenylsulfinyl derivatives.[7] In the present work, we report on a highly diastereoselective addition of methylmagnesium bromide to isopropylsulfinylimime. The synthetic value of this approximation is further demonstrated by the enantioselective synthesis of the potent calcimimetic (*R*)-(+)-NPS R-568 (**1**).

Calcimimetics are small organic molecules which activate specifically the calcium-sensing receptor (CaSR), in the same way as extracellular Ca^{2+}, and as such have great potential as innovative medical approach for the treatment of primary and

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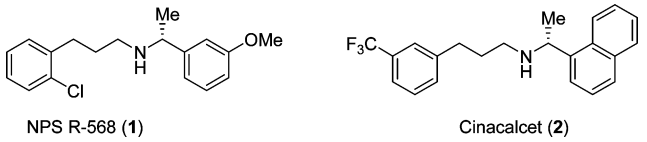
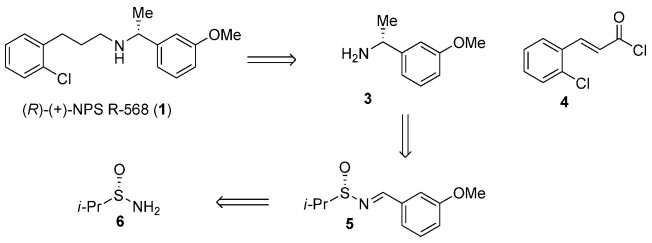


FIGURE 2. Structural formulas of calcium-sensing receptor calcimimetics NPS R-568 (**1**) and cinacalcet (**2**).

SCHEME 1. Retrosynthetic Analysis of (*R*)-(+)-NPS R-568 (1)

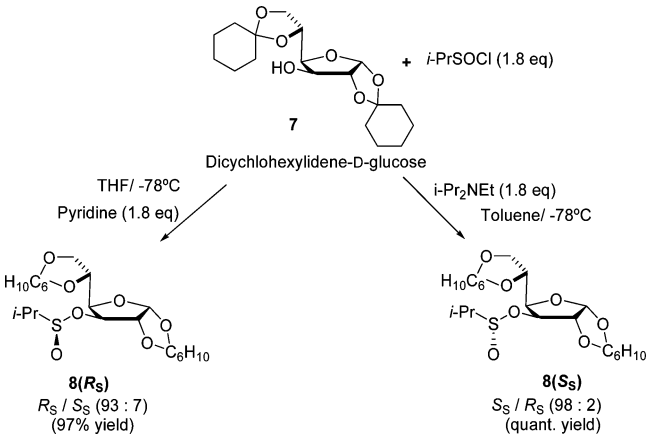


secondary hyperparathyroidism.[8] Indeed, cinacalcet (**2**, Figure 2), a compound with improved metabolic profile, has recently been launched in several countries for the treatment of hyperparathyroidism in patients with chronic kidney disease who are on dialysis and for the treatment of hypercalcemia in patients with parathyroid carcinoma.

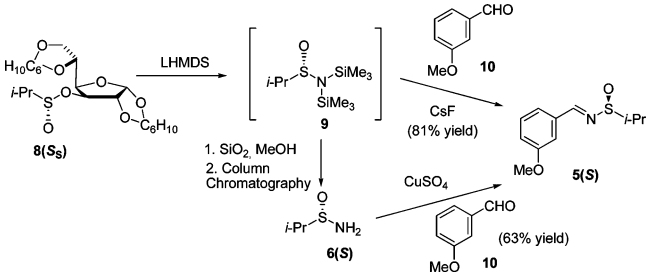
Clinical studies with the calcimimetic NPS R-568 (**1**) have shown that its biological activity is intimately related with the configuration of the chiral center. Accordingly, the (*R*)-(+)-NPS R-568, which is the eutomer, is 10−100 times more potent than the (*S*)-(−)-NPS distomer.[9] A retrosynthetic analysis of (*R*)-(+)-NPS R-568 (**1**), Scheme 1, shows that it can be easily obtained from the commercially available 3-(2-chlorophenyl)-2-propenyl chloride **4** and (*R*)-1-(3-methoxyphenyl)ethylamine **3**. The preparation of enantiomerically pure amine with the *R* absolute configuration at C1 can be done from (*S*)-isopropylsulfinylimine **5** derived from (*S*)-isopropylsulfinamide **6**.

The asymmetric synthesis of isopropylsulfinamide **6** can be done in an enantiodivergent manner using as sulfinylating agents sugar based sufinate esters **8(*R*$_S$)** and **8(*S*$_S$)**, prepared using our DAG methodology (Scheme 2).[10] Noteworthy, in this case we have found that the glucose-derived dicyclohexylidene-D-glucose (DCG) **7**, obtained in a single step from D-glucose, gave better chemical yields and diastereoselectivity than the diacetone-D-glucose. Accordingly, the condensation of 1 molar equiv of secondary carbinol **7** with 1.8 molar equiv of racemic *i*-PrSOCl in THF using pyridine as base afforded the isopropylsulfinate ester **8(*R*$_S$)** in 97% chemical yield and 86% de (Scheme 2). As expected, employing toluene as solvent, and using exactly the same conditions than before, but changing the base from

SCHEME 2. Diastereodivergent Approach for the Synthesis of 8(*S*$_S$) and 8(*R*$_S$) DCG Isopropyl Sulfinate Esters



SCHEME 3. Synthesis of *N*-Isopropylsulfinylimine 9(*S*)



pyridine to *i*-Pr$_2$NEt, afforded diastereoselectively isopropyl sulfinate ester **8(*S*$_S$)** in quantitative yield and 96% de (Scheme 2). Additionally, the DCG isopropylsulfinate esters **8** were stable, as no decomposition of these sulfinates was detected after months at 4 °C.

The preparation of *N*-sulfinylimine **5(*S*)** has been done in two different ways, Scheme 3. The action of LiHMDS on sulfinate ester **8(*S*$_S$)** leading to the *N*,*N*-bis-trimethylsilylsulfinamide **9**, followed by treatment with 3-methoxybenzaldehyde (**10**) in THF, in the presence of a suspension of CsF, afforded, after a single recrystallization, enantiomerically pure (as shown by HPLC analysis) sulfinylimine **5(*S*)** in good chemical yield. Alternatively, the preparation of **5(*S*)** can be done in two steps, through isolation of isopropylsulfinamide **6(*S*)**, followed by imination with 3-methoxybenzaldehyde **10** using $CuSO_4$ as dehydrating agent, although in lowest chemical yield.

It is worth of mention that the synthesis of *N*-sulfinylimine **5(*S*)**, using sulfinate ester **8(*S*$_S$)** as sulfinylating agent, takes place efficiently under very smooth reaction conditions as compared with the procedures reported for the synthesis of *p*-toluenesulfinylimines **I** and the 2-methylpropane-2-sulfinylimines **II**. Accordingly, the complete transformation of sulfinate ester **8(*S*$_S$)** to the silylated sulfinamide derivative **9** takes place at 0 °C in only 5 min, and through the condensation of 3-methoxybenzaldehyde, the final sulfinylimine **5(*S*)** has been obtained in high chemical yield after 1 h. As the addition of methyl Grignard on sulfinylimine **5(*S*)** constitutes the key step of the approach, a systematic study was conducted using different solvents (THF, toluene, CH_2Cl_2), temperatures (from −78 °C to rt), as well as number of molar equivalents of the Grignard reagent.

From this study, it was found that using 2 molar equiv of methyl Grignard in toluene at −78 °C afforded sulfinamide **11**-

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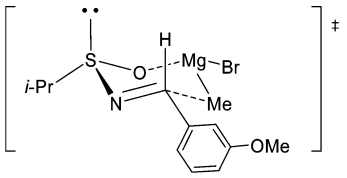
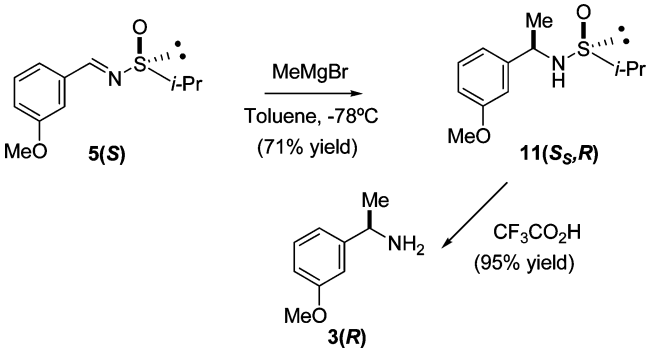


FIGURE 3. Explanative model for the preferred formation of **11(S_S,*R*)**.

SCHEME 4. Synthesis of (*R*)-1-(3-Methoxyphenyl)ethylamine [3(*R*)]



(S_S,*R*) as a single diastereoisomer. This result indicates that the nucleophilic attack of the small methyl Grignard takes place on the iminic carbon and not on the sulfinyl sulfur, probably as consequence of steric and electronic factors.[11] Treatment of compound **11(S_S,*R*)** with trifluoroacetic acid in methanol provokes the desulfinylation of the sulfinamide and provides the desired product as trifluoroacetate ammonium salt in quantitative yield (Scheme 4). Purification of the product on an ion-exchange column (SCX) afforded enantiomerically pure (*R*)-1-(3-methoxyphenyl)ethylamine ($[\alpha]_D$ = +21.7 (*c* 0.3, MeOH) (lit.[12] +17.6 (*c* 0.2, MeOH)). Based on the absolute configuration of the final amine, the stereoselectivity of the addition step can be rationalized by invoking a coordinated Zimmerman−Traxler like model, where the approximation of the nucleophile takes place from the less hindered face of the imine, Figure 3.

Condensation of (*R*)-1-(3-methoxyphenyl)ethylamine **3(*R*)** with 3-(2-chlorophenyl)-2-propenyl chloride **4** in the presence of sodium carbonate afforded amide **12(*R*)** in excellent yield. Finally, reduction of the α,β-insaturated amide **12(*R*)**, followed by treatment with DIBAL-H in THF, afforded the calcimimetic (*R*)-(+)-NPS R-568 (**1**) in enantiopure form and in good chemical yield, Scheme 5.

In conclusion, the results presented in this work show that besides the advantage of lower molecular weight, the isopropyl sulfinyl group does confer high chemical reactivity, better enantiomeric discrimination than the *p*-tolylsulfinyl group, and equal or even much better enantiomeric discrimination than the most popular *tert*-butyl group. The usefulness of this new chiral controller has been demonstrated by a highly enantioselective synthesis of arylamines. The synthetic utility of the approach has been demonstrated by an expeditive synthesis of the calcimimetic drug (*R*)-(+)-NPS R-568 (**1**).

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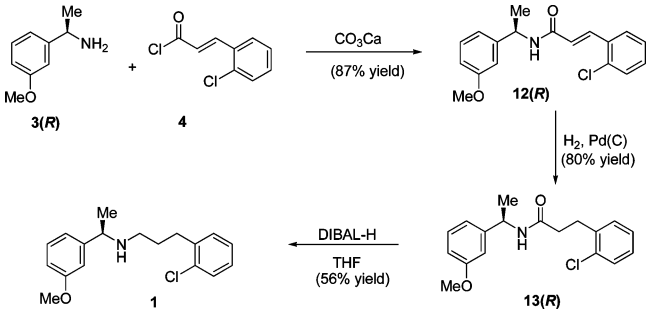
SCHEME 5. Synthesis of Calcimimetic (*R*)-(+)-NPS R-568



Experimental Section

General methods and experimental details for the synthesis of sulfinate ester **8(S_S)** and sulfinamide **6(*S*)** can be found in the Supporting Information.

(*S*)-*N*-(3-Methoxybenzylidene)isopropylsulfinamide, 5(*S*). Method A. To a solution of sulfinate ester **8(S_S)** (6.7 g, 14.7 mmol) in THF (20 mL) at 0 °C was added a 1 M LiHMDS solution in THF (17.6 mL, 17.6 mmol). The reaction mixture was stirred for 5 min and transferred via cannula to a second flask containing 3-methoxybenzaldehyde (3.36 mL, 22.05 mmol) and CsF (2.7 g, 17.6 mmol) in THF (15 mL). After being stirred for 30 min at room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution, and the aqueous layer was extracted with AcOEt (4 × 40 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution and with saturated NaCl aqueous solution and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography ($AcOEt/Cl_2CH_2$ 1:30−1:20), to give **5(*S*)** (2.7 g, 81% yield) as a white solid in 90% ee. Enantiopure sulfinylimine was obtained after crystallyzation from hexanes.

Method B. To a suspension of $CuSO_4$ (10.8 g, 67.67 mmol) in CH_2Cl_2 (30 mL) at room temperature was added a solution of (*S*)-isopropanesulfinamide **6(*S*)** (1.2 g, 11.22 mmol) in CH_2Cl_2 (15 mL) and then 3-methoxybenzaldehyde (1.36 mL, 11.22 mmol). After being stirred overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with AcOEt (4 × 40 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography ($AcOEt/Cl_2CH_2$ 1:30−1:20), to give enantiopure **5(*S*)** (1.6 g, 63.4% yield) as a white solid: mp 54 °C; $[\alpha]^{20}_D$ +77 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.49−7.43 (m, 3H), 7.11−7.09 (m, 1H), 3.89 (s, 3H), 3.00 (m, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 160.0, 135.3, 130.0, 122.6, 119.0, 113.0, 55.4, 53.9, 14.8, 13.5; HRMS *m*/*e* calcd for $C_{11}H_{16}NO_2S$ $(M + H)^+$ 226.0901, found 226.0895.

The enantiomeric ratio was determined by HPLC analysis using chiralpack OJ column: flow rate 0.8 mL/min, *i*-PrOH/hexane 3:97, 30 °C, t_S = 15.0 min (**5*S***) and t_R = 19.7 min (**5*R***).

(S_S,*R*)-*N*-[1-(3-Methoxyphenyl)ethyl]isopropylsulfinamide, 11(S_S,*R*). To a solution of sulfinylimine **5(*S*)** (1.0 g, 4.42 mmol) in toluene (15 mL) at −78 °C was added a 1.4 M MeMgBr solution (6.35 mL, 8.89 mmol) in THF. The reaction mixture was slowly warmed to room temperature and stirred overnight. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the aqueous layer was extracted with AcOEt (3 × 40 mL). The organic layer was washed with saturated aqueous NaCl solution and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (AcOEt/hexanes 1:1−1:20), to give enantiopure **11(S_S,*R*)** (760 mg, 71.7% yield) as a colorless oil: $[\alpha]^{20}_D$ +112.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.26 (m, 1H), 6.96−

6.92 (m, 2H), 6.85−6.83 (m, 1H), 4.60−4.57 (m, 1H), 3.81 (s, 3H), 3.61 (bs, 1H), 2.75 (m, *J*=6.9 Hz, 1H), 1.56 (d, *J*=6.8 Hz, 3H), 1.28 (d, *J*=6.9 Hz, 3H), 1.27 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 140.2, 129.9, 118.9, 114.6, 111.9, 55.3, 51.5, 50.6, 22.8, 21.0, 17.4; HRMS *m*/*e* calcd for $C_{12}H_{20}NO_2S$ (M + H)$^+$ 242.1214, found 242.1203.

(*R*)-1-(3-Methoxyphenyl)ethylamine, 3(*R*). To a solution of sulfinamide **11(*S*$_S$,*R*)** (765 mg, 3.17 mmol) in MeOH (20 mL) at 0 °C was added CF_3CO_2H (1.82 mL, 23.77 mmol), and the reaction mixture was slowly warmed to room temperature. After the mixture was stirred overnight, the solvent was removed under reduced pressure to give the corresponding ammonium salt in quantitative yield. The residue was passed through a cation-exchange column (Isolute SPE SCX-2) to give the amine **3(*R*)** (453 mg, 95%) as a colorless oil: $[\alpha]^{20}_D$ +21.7 (*c* 0.3, MeOH) (lit.[12a] +17.6 (*c* 0.2, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.25 (m, 1H), 6.95−6.93 (m, 1H), 6.81−6.79 (m, 1H), 4.11 (q, *J* = 6.6 Hz, 1H), 3.84 (s, 3H), 1.69 (bs, 2H), 1.41 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 149.5, 129.5, 118.1, 112.1, 111.4, 55.2, 51.35, 25.57; HRMS *m*/*e* calcd for $C_9H_{14}NO$ (M + H)$^+$ 152.1075, found 152.1069.

3-(2-Chlorophenyl)-*N*-[(*R*)-1-(3-methoxyphenyl)ethyl]-2-propenamide, 12(*R*). To a stirred solution of amine **3(*R*)** (136 mg, 0.89 mmol) in CH_2Cl_2 (15 mL) were added 3-(2-chlorophenyl)-2-propenyl chloride (180.8 mg, 0.89 mmol) and Na_2CO_3 (95.33 mg, 0.89 mmol) at room temperature. After the mixture was stirred overnight, water (20 mL) was added and the solution extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash chromatography (AcOEt/hexanes 1:5) to give the amide **12(*R*)** (244 mg, 87% yield) as an enantiopure white solid: mp 145−146 °C; $[\alpha]^{20}_D$ +33 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 15.6 Hz, 1H), 7.57 (dd, *J* = 2.0 and 7.3 Hz, 1H), 7.43 (dd, *J* = 1.7 and 7.5 Hz, 1H), 7.32−7.23 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.94−6.93 (m, 1H), 6.85 (dd, *J* = 2.5 and 8.2 Hz, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 5.89 (br d, *J* = 7.5 Hz, 1H), 5.27 (m, *J* = 7.3 Hz, 1H), 3.84 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 159.9, 144.7, 137.2, 134.8, 133.2, 130.4, 130.2, 129.8, 127.6, 126.9, 123.6, 118.5, 112.7, 112.4, 55.3, 49.1, 21.6; HRMS *m*/*e* calcd for $C_{18}H_{18}ClNO_2$ (M)$^+$ 315.1026, found 315.1030.

3-(2-Chlorophenyl)-*N*-[(*R*)-1-(3-methoxyphenyl)ethyl]propanamide, 13(*R*). To a stirred solution of enamide **12(*R*)** (100 mg, 0.32 mmol) in a 1:1 AcOEt/MeOH solvent mixture (4 mL) was added Pd(C) cat. and stirred under hydrogen pressure for 3 h. The reaction mixture was filtered over Celite with MeOH. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (AcOEt/hexanes 1:2) to give the amide **13(*R*)** (80 mg, 80% yield) as a white solid: mp 96 °C; $[\alpha]^{20}_D$ +47 (c 1.0, $CHCl_3$) [lit.[12a] $[\alpha]^{20}_D$ +45.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.20 (m, 5H), 6.82−6.80 (m, 3H), 5.51 (bd, *J* = 7.0 Hz, 1H), 5.09 (m, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 1.42 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 159.8, 144.7, 140.8, 136.0, 134.4, 129.7, 128.5, 128.4, 126.2, 118.4, 112.5, 112.3, 55.2, 48.7, 38.6, 31.7, 21.6; HRMS *m*/*e* calcd for $C_{18}H_{21}NO_2$ (M + H − Cl)$^+$ 283.1572, found 283.1570.

3-(2-Chlorophenyl)-*N*-[(*R*)-1-(3-methoxyphenyl)ethyl]-1-propanamine, 1(*R*). To a stirred solution of amide **13(*R*)** (80 mg, 0.25 mmol) in CH_2Cl_2 (2 mL) was added a 1 M DIBAL solution in THF (0.96 mL, 0.96 mmol) at room temperature. After being stirred overnight, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (3 mL). The mixture was filtered through a Celite pad, the filtrate was concentrated in vacuo, and the residue was purified on a cation-exchange column (Isolute SPE SCX-2) to give **1(*R*)** as a yellow oil (42.6 mg, 56%): $[\alpha]^{20}_D$ +39.1 (*c* 1.0, $CHCl_3$) [lit.[12a] $[\alpha]^{20}_D$ +38.6 (*c* 1.1, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.16 (m, 5H), 6.93−6.91 (m, 2H), 6.79 (ddd, *J* = 8.3, 2.4 and 0.9 Hz, 1H), 3.83 (s, 3H), 3.76 (q, *J* = 6.5 Hz, 1H), 2.70−2.50 (m, 4H), 1.85−1.80 (m, 2H), 1.38 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 147.0, 142.1, 129.4, 128.3, 128.2, 125.7, 119.0, 112.3, 112.1, 58.4, 55.2, 47.3, 33.6, 31.7, 24.1; HRMS *m*/*e* calcd for $C_{18}H_{22}NO$ (M − Cl)$^+$ 268.1701, found 268.1697.

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Supporting Information Available: General methods and experimental details for the synthesis of **8(*S*$_S$)** and **6(*S*)** are described. Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **1**, **3**, **5(*S*)**, **11(*S*$_S$,*R*)**, **12(*R*)**, and **13(*R*)** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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